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Correlation between some parameters of lead absorption and lead intoxication

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Waldron, H. A. (1971). *Brit. J. industr. Med.*, **28**, 195-199. **Correlation between some parameters of lead absorption and lead intoxication.** Use has been made of data collected over a number of years from workers exposed to a lead hazard in a motor-car factory. The correlations between various parameters of lead absorption and lead intoxication were computed, including blood and urine lead concentrations, urinary coproporphyrin, ALA and PBG concentrations, and haemoglobin concentration. In all, 15 correlation coefficients were calculated, of which only six showed a statistically significant result (i.e., $P < 0.05$). These six were blood lead and urine lead ($r = 0.38$, $P < 0.001$), urine lead and coproporphyrin ($r = 0.42$, $P < 0.001$), urine lead and ALA ($r = 0.43$, $P < 0.001$), coproporphyrin and ALA ($r = 0.75$, $P < 0.001$), ALA and PBG ($r = 0.49$, $P < 0.001$), and urine lead and PBG ($r = 0.19$, $P < 0.05$).

The laboratory tests which are used in the control of an industrial lead hazard fall into one of two categories, those which measure lead absorption and those which give an index of lead intoxication. The former group includes blood and urine lead determinations and the latter, determination of the level of excretion of δ-aminolevulinic acid (ALA) or coproporphyrin in the urine, or haemoglobin estimations.

Several studies have been made correlating the different tests with each other (Bashour, 1954; Brooks, 1951; Cramér and Selander, 1965; de Bruin and Hoolboom, 1967; Gibson, Mackenzie, and Goldberg, 1968; Haeger-Aronsen, 1960; Meek, Mooney, and Harrold, 1948; Selander and Cramér, 1970; Selander, Cramér and Halberg, 1966; Singerman, 1964) or with the degree of exposure to which the individual workman is subjected (Williams, King, and Walford, 1969). As the results from these studies have not always been in agreement, data obtained over a number of years from workers exposed to lead in a motor-car factory have been analysed and correlated and the results are discussed in relation to earlier findings.

Definition of terms

The terms 'lead absorption' and 'lead intoxication' are not always used consistently and it is possible that one author will use the term 'lead absorption' to refer to the condition which another would describe as lead intoxication. A third author may use the term 'lead poisoning' to describe either lead absorption or intoxication, or both. There is little doubt that this inconsistency of usage leads to confusion in the literature and so it was thought appropriate to define the terms as used here. The definitions given are closely modelled on those originally proposed by Belknap (1949) and Zielhuis (1961).

Lead absorption

This refers to the uptake of lead by the subject from his environment by any route. Absorption may, or may not, be sufficient to give rise to lead intoxication.

Lead intoxication

This may be either pharmacological or clinical.

Pharmacological intoxication may be said to be present when there is evidence that absorbed lead is interfering with some metabolic process in the body.

Most often this will show as an interference with haem synthesis and will be detected by the excessive excretion of haem precursors in the urine. There are no clinical symptoms at this stage.

Clinical intoxication occurs when the patient is aware of symptoms or the clinician can detect objective signs of disease.

The term 'lead poisoning' is not used in this paper but by definition it is considered to be equivalent to clinical lead intoxication.

Materials and methods

Use has been made of the results of analyses performed over a number of years on lead workers employed in a motor-car factory. The men were employed on different jobs in the lead-working area and so it is reasonable to suppose that the degree of exposure was not constant for the group as a whole. No measurements were made of individual exposure although routine lead-in-air tests were performed at monthly intervals throughout the entire period. These showed that the atmospheric lead content was never higher than 80 $\mu g/m^3$ or less than 45 $\mu g/m^3$.

The tests performed included blood and urine lead estimations, haemoglobin estimation, urinary coproporphyrin (semiquantitative and quantitative), ALA, and porphobilinogen (PBG) estimations. Not all these tests were made on each worker so that there is some disparity between the total number of observations (n), as shown in the Table. No worker is included more than once in each group so that n represents both the total number of individuals as well as the total number of observations. All the methods used have been described elsewhere (de Kretser and Waldron, 1963).

All the urine analyses were made on spot samples. No correction factors were applied but samples with a specific gravity of less than 1010 were discarded. The use of spot samples for urine analysis and the various correction factors suggested to correct results from spot samples have been fully discussed by other workers (Ellis, 1966; Molyneux, 1964; Williams *et al.* 1969) and will not be pursued here. The evidence suggests, however, that the errors arising from the use of spot samples are not significantly greater than when 24-hour urine specimens are used, and that none of the correction factors is completely satisfactory.

Results

Correlation coefficients (r) were computed between all the available parameters and the results are shown in the Table. Where r had a statistically significant value ($P \leqslant 0.05$) regression equations were computed and graphs were drawn from these equations (Figs. 1 to 6).

Significant correlations were found in six instances, that is, between blood and urine lead; urine lead and ALA, PBG, and quantitative coproporphyrin; ALA and quantitative coproporphyrin; and ALA and PBG. Of these six, the correlation between urine lead and PBG was less significant (as shown by the value for P) than the other five.

TABLE

CORRELATION COEFFICIENTS FOR VARIOUS PARAMETERS OF LEAD ABSORPTION AND LEAD INTOXICATION

Test	r	n	P
Blood lead *v* urine lead	0·38	554	<0·001
Blood lead *v* Hb	−0·03	554	NS
Blood lead *v* Copro (semi)	0·02	554	NS
Urine lead *v* Hb	−0·07	554	NS
Urine lead *v* Copro (semi)	0·02	554	NS
Urine lead *v* Copro (quant)	0·42	85	<0·001
Urine lead *v* ALA	0·43	132	<0·001
Urine lead *v* PBG	0·19	125	<0·05
Hb *v* Copro (quant)	−0·01	85	NS
Hb *v* ALA	−0·18	137	NS
Hb *v* PBG	−0·12	137	NS
Copro (quant) *v* ALA	0·75	85	<0·001
Copro (quant) *v* PBG	0·07	78	NS
Copro (semi) *v* Hb	−0·07	554	NS
ALA *v* PBG	0·49	145	<0·001

Copro = coproporphyrin.

In addition to the correlations shown in the Table, the correlations between each of the parameters measured and the length of exposure to lead were computed. The length of exposure was obtained from each individual's record card and expressed to the nearest calendar month. None of these correlations was significant.

For completeness, the value for r between the semiquantitative and quantitative coproporphyrin

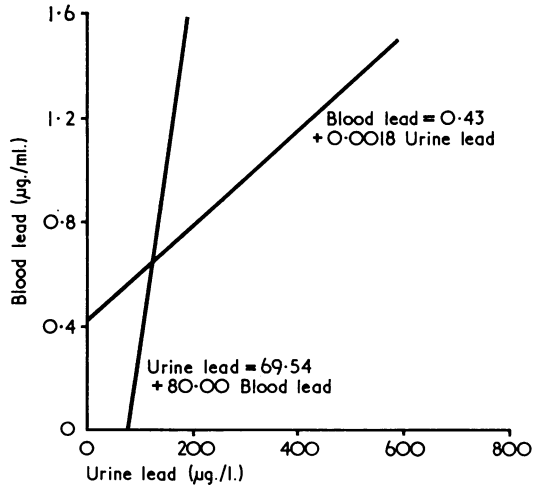


FIG. 1. Regression lines: blood lead on urine lead; urine lead on blood lead.

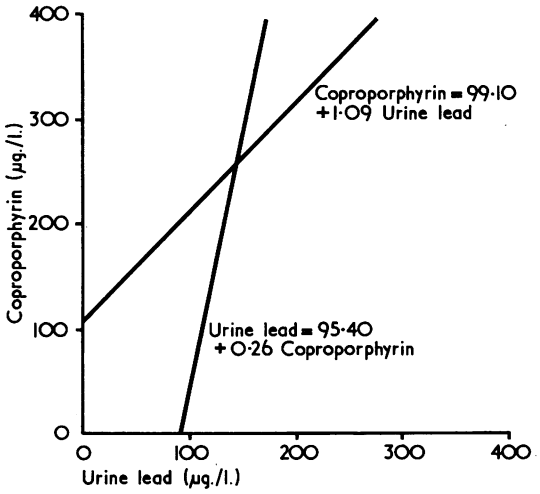


FIG. 2. Regression lines: coproporphyrin on urine lead; urine lead on coproporphyrin.

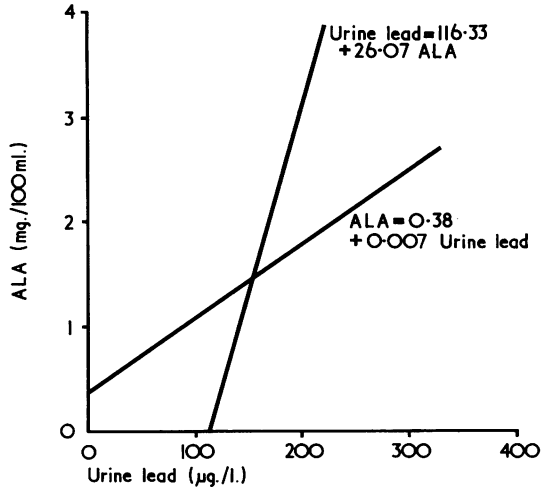


FIG. 4. Regression lines: ALA on urine lead; urine lead on ALA.

estimations was computed. This gave $r = 0{\cdot}82$, $n = 93$, and $P < 0{\cdot}001$.

Discussion

Relationship between tests of absorption

The correlation between blood lead and urine lead values was found to be statistically significant in this study, confirming results previously reported by Selander and Cramér (1970). Selander *et al.* (1966), and Williams *et al.* (1969).

Relationship between tests indicating intoxication

The results presented here show that of the tests used to indicate pharmacological intoxication, ALA and PBG, and ALA and coproporphyrin correlated significantly with each other, confirming the general experience of other workers (Bashour, 1954; Haeger-Aronsen, 1960; Cramér and Selander, 1965; de Bruin and Hoolboom, 1967; Gibson *et al.*, 1968; Williams *et al.*, 1969). On the other hand, PBG and coproporphyrin did not correlate significantly, nor were any of the correlations between haemoglobin

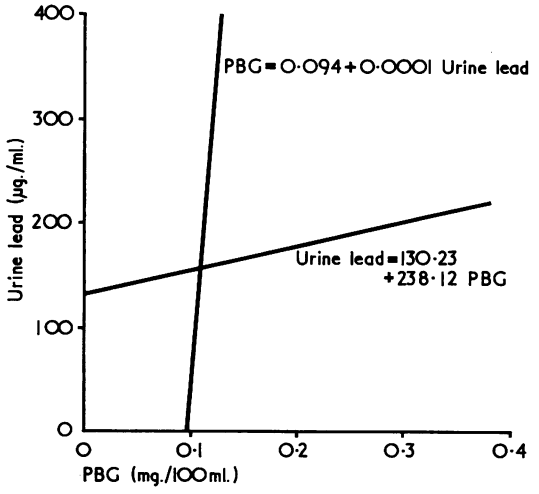


FIG. 3. Regression lines: urine lead on PBG; PBG on urine lead.

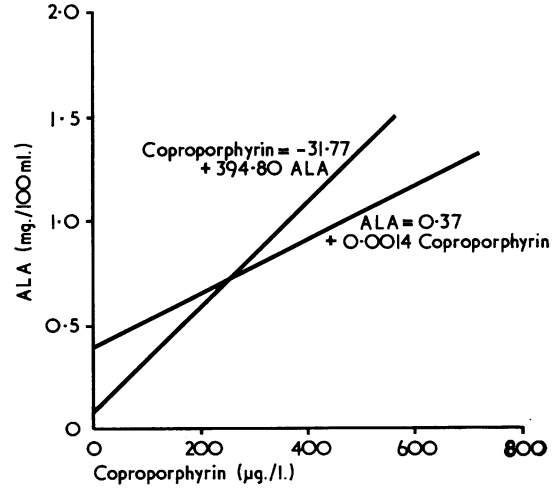


FIG. 5. Regression lines: ALA on coproporphyrin; coproporphyrin on ALA.

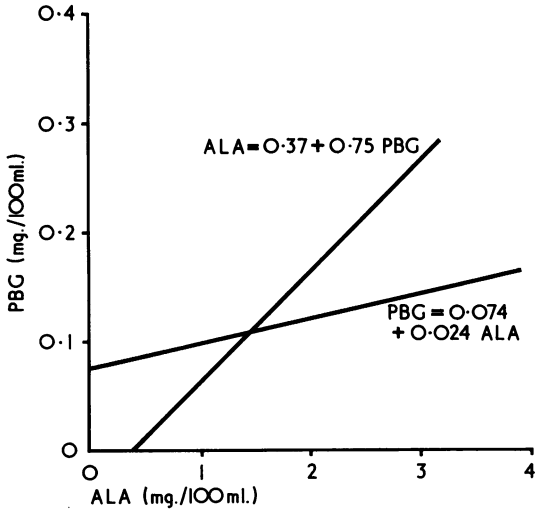


FIG. 6. Regression lines: PBG on ALA; ALA on PBG.

values and the other parameters of intoxication significant.

The statistical significance, or otherwise, of the correlation between haemoglobin levels and other parameters of pharmacological intoxication has been variously reported in the past. Bashour (1954) and Gibson *et al.* (1968) found the correlation between haemoglobin and coproporphyrin to have statistical significance, and the latter workers also found the relationship between haemoglobin and ALA significant. By contrast, Haeger-Aronsen (1960) found no significant correlation between haemoglobin and ALA in her study, a finding confirmed recently by Williams *et al.* (1969).

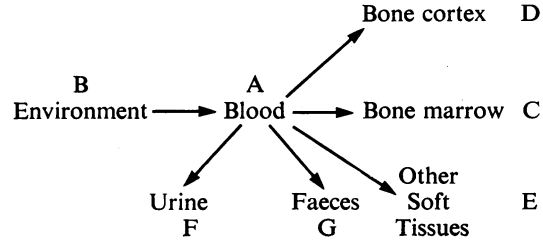
It has been shown that the mean haemoglobin level of a group of lead workers may not differ from that of a control group despite the excretion of considerable amounts of coproporphyrin in the urine of the lead workers (Waldron, 1964), and in the present study the mean haemoglobin levels of those groups of workers in whom haemoglobin was correlated with coproporphyrin, or with ALA and PBG, were 96·1% (SD 5·4) and 95·9% (SD 5·3) respectively, that is, normal values. On the other hand, the mean coproporphyrin and ALA values were considerably raised above normal ($\text{coproporphyrin}_{\text{mean}} = 282$ µg/l, SD 393, $\text{ALA}_{\text{mean}} = 1{\cdot}46$ mg/100 ml, SD 2·01) although PBG was not raised ($\text{PBG}_{\text{mean}} = 0{\cdot}11$ mg/100 ml, SD 0·10). These findings indicate that the interference by lead with haem synthesis must be on a large scale to cause the haemoglobin level to be lowered. Thus, in workers with a low level of industrial exposure one might not expect to find any significant correlation between the excretion of haem precursors and haemoglobin levels since the latter will not be deviated markedly from normal. In severely affected individuals, on the other hand, where haemoglobin levels are depressed, then it may be that correlations will emerge.

Relationship between tests of absorption and intoxication

The results from the present investigation are unusual in that whereas significant correlations were obtained between some parameters of absorption and intoxication (urine lead and ALA and quantitative coproporphyrin), others were not significantly correlated (urine lead and semiquantitative coproporphyrin, blood lead and semiquantitative coproporphyrin). This is in contrast with the general experience of other workers who have found that the correlations between these various parameters of absorption and intoxication are either *all* significant (Bashour, 1954: Singerman, 1964; Cramér and Selander, 1965; Selander *et al.*, 1966; Williams *et al.*, 1969) or *all* non-significant (Gibson *et al.*, 1968). The poor correlation between blood lead levels and haemoglobin concentrations reported here confirms the findings of the earlier comprehensive study of Williams (1966) and that author's more recent report (Williams *et al.*, 1969).

Gibson and her colleagues suggested that the lack of correlation between absorption and intoxication is not surprising, particularly in view of the fact that individuals may vary in their susceptibility to toxic agents. In view of this statement, and because of the ambivalent findings in the current study, it is worth considering whether *a priori* any relationship between lead absorption and pharmacological intoxication is to be expected.

Following absorption, lead may be considered to be distributed in the organism in the following way



The blood lead concentration will be a function of the amount of lead absorbed from the environment less that deposited in the bone cortex and the soft tissues and that excreted in the urine and faeces. This statement may be represented in the form of an equation:

$$A = B - ((F + G) + (C + D + E))$$

It has been shown that the kinetics of the uptake and excretion of lead varies from tissue to tissue (Castellino and Aloj, 1964), the uptake and excretion

of lead by bone being extremely slow compared with that by soft tissues. Moreover, the concentration of lead found in different soft tissues varies considerably after a dose of ^{210}Pb, renal tissue having a considerably higher concentration than other tissues (liver, lung, spleen, heart, and striated muscle). In addition, the concentration of lead in the bone marrow is many times higher than the blood lead concentration (Westerman, Pfitzer, Ellis, and Jensen, 1965). It is likely to be the concentrations of lead in the liver and the bone marrow which will be the most important in determining the development of anaemia since these are the sites respectively of porphyrin synthesis and haemoglobinization of the red cell, and it may be seen from the equation above that these concentrations cannot be predicted accurately from a knowledge of the blood lead concentration as the value of A may be constant despite considerable variation in the values in the right-hand bracket. Similarly, the urine lead concentration (F) may be constant despite wide fluctuations in the other variables concerned. There seems no reason on *a priori* grounds, therefore, to suppose that the blood or urine lead values will show any relationship to the degree of pharmacological intoxication since neither can be taken as an accurate reflection of the amount of pharmacologically active lead present in the body. The fact that most authorities report findings contrary to this view is, from the industrial hygienist's point of view, extremely fortunate.

Choice of test

The choice of test used to monitor a lead hazard is dependent on a number of factors. Broadly speaking, there are two schools of thought, those who advocate monitoring absorption with a view to keeping the blood lead below the level at which intoxication is likely to occur, and those who advocate detecting signs of pharmacological intoxication regardless of the degree of absorption. It has been shown recently that all parameters, with the exception of haemoglobin levels, correlate very well with individual exposure (Williams *et al.*, 1969) and, generally, tests of absorption have been shown to correlate well with tests of pharmacological intoxication. There would seem, therefore, to be little to choose between the various tests described. The choice, then, might depend on factors such as reliability, simplicity of the method, and its cost relative to the other tests. Using these criteria, no test would seem to be more suitable as a screening procedure than the simple semiquantitative coproporphyrin estimation.

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References

Bashour, F. A. (1954). Urinary uroporphyrin, porphobilinogen and coproporphyrin excretion in lead-exposed workers. *J. Lab. clin. Med.*, **44**, 764.

Belknap, E. L. (1949). Differential diagnosis of lead poisoning. Accepted laboratory criteria. *J. Amer. med. Ass.*, **139**, 818-823.

Brooks, A. L. (1951). An appraisal of a urinary porphyrin test in detection of lead absorption. *Industr. Med. Surg.*, **20**, 390-392.

Castellino, N., and Aloj, S. (1964). Kinetics of the distribution and excretion of lead in the rat. *Brit. J. industr. Med.*, **21**, 308-314.

Cramér, K., and Selander, S. (1965). Studies in lead poisoning. Comparison between different laboratory tests. *Brit. J. industr. Med.*, **22**, 311-314.

de Bruin, A., and Hoolboom, H. (1967). Early signs of lead-exposure. A comparative study of laboratory tests. *Brit. J. industr. Med.*, **24**, 203-212.

de Kretser, A. J., and Waldron, H. A. (1963). Urinary delta amino-laevulinic acid and porphobilinogen in lead-exposed workers. *Brit. J. industr. Med.*, **20**, 35-40.

Ellis, R. W. (1966). Urinary screening tests to detect excessive lead absorption. *Brit. J. industr. Med.*, **23**, 263-281.

Gibson, S. L. M., Mackenzie, J. C., and Goldberg, A. (1968). The diagnosis of industrial lead poisoning. *Brit. J. industr. Med.*, **25**, 40-51.

Haeger-Aronsen, B. (1960). Studies on urinary excretion of delta-aminolaevulic acid and other haem precursors in lead workers and lead-intoxicated rabbits. *Scand. J. clin. Lab. Invest.*, **12**, Suppl. 47.

Meek, S. F., Mooney, T., and Harrold, G. C. (1948). Urinary porphyrins in lead poisoning. *Industr. Med.*, **17**, 469-471.

Molyneux, M. K. B. (1964). Use of single urine samples for the assessment of lead absorption. *Brit. J. industr. Med.*, **21**, 203-209.

Selander, S., and Cramér, K. (1970). Interrelationships between lead in blood, lead in urine, and ALA in urine during lead work. *Brit. J. industr. Med.*, **27**, 28-39.

——, ——, and Hallberg, L. (1966). Studies in lead poisoning. Oral therapy with penicillamine: relationship between lead in blood and other laboratory tests. *Brit. J. industr. Med.*, **23**, 282-291.

Singerman, A. (1964). Studies on lead poisoning in Argentina. *Arch. environm. Hlth*, **9**, 464-472.

Waldron, H. A. (1964). Plasma porphyrins in lead workers. *Brit. J. industr. Med.*, **21**, 315-317.

Westerman, M. P., Pfitzer, E., Ellis, L. D., and Jensen, W. N. (1965). Concentrations of lead in bone in plumbism. *New Engl. J. Med.*, **273**, 1246-1250.

Williams, M. K. (1966). Blood lead and haemoglobin in lead absorption. *Brit. J. industr. Med.*, **23**, 105-111.

——, King, E., and Walford, J. (1969). An investigation of lead absorption in an electric accumulator factory with the use of personal samplers. *Brit. J. industr. Med.*, **26**, 202-216.

Zielhuis, R. L. (1961). Maximum allowable limits in biological materials in the prevention of inorganic lead poisoning. *Pure and appl. Chem.*, **3**, 292-302.

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